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ORIGINAL RESEARCH

Kurtosis and Skewness of Density Histograms on Inspiratory and Expiratory CT Scans in Smokers

Tsuneo Yamashiro,[1,2] Shin Matsuoka,[3] Raúl San José Estépar,[4] Brian J. Bartholmai,[5] Alejandro Diaz,[6,7] James C. Ross,[4] Sadayuki Murayama,[2] Edwin K. Silverman,[6,8] Hiroto Hatabu,[1] and George R. Washko[6]

Center for Pulmonary Functional Imaging, Brigham and Women's Hospital, Boston, MA, USA,[1] Department of Radiology, University of the Ryukyus, Nishihara, Okinawa, Japan,[2] Department of Radiology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan,[3] Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, MA, USA,[4] Department of Radiology, Mayo Clinic, Rochester, MN, USA,[5] Pulmonary and Critical Care Division, Brigham and Women's Hospital, Boston, MA, USA,[6] Pontificia Universidad Catolica de Chile, Santiago de Chile, Chile,[7] Channing Laboratory, Brigham and Women's Hospital, Boston, MA, USA[8]

The aim of this study is to evaluate the relationship between lung function and kurtosis or skewness of lung density histograms on computed tomography (CT) in smokers. Forty-six smokers (age range 46−81 years), enrolled in the Lung Tissue Research Consortium, underwent pulmonary function tests (PFT) and chest CT at full inspiration and full expiration. On both inspiratory and expiratory scans, kurtosis and skewness of the density histograms were automatically measured by open-source software. Correlations between CT measurements and lung function were evaluated by the linear regression analysis. Although no significant correlations were found between inspiratory kurtosis or skewness and PFT results, expiratory kurtosis significantly correlated with the following: the percentage of predicted value of forced expiratory volume in the first second (FEV_1), the ratio of FEV_1 to forced vital capacity (FVC), and the ratio of residual volume (RV) to total lung capacity (TLC) (FEV_1%predicted, R = −0.581, p < 0.001; FEV_1/FVC, R = −0.612, p < 0.001; RV/TLC, R = 0.613, p < 0.001, respectively). Similarly, expiratory skewness showed significant correlations with PFT results (FEV_1%predicted, R = −0.584, p < 0.001; FEV_1/FVC, R = −0.619, p < 0.001; RV/TLC, R = 0.585, p < 0.001, respectively). Also, the expiratory/inspiratory (E/I) ratios of kurtosis and skewness significantly correlated with FEV_1%predicted (p < 0.001), FEV_1/FVC (p < 0.001), RV/TLC (p < 0.001), and the percentage of predicted value of diffusing capacity for carbon monoxide (kurtosis E/I ratio, p = 0.001; skewness E/I ratio, p = 0.03, respectively). We conclude therefore that expiratory values and the E/I ratios of kurtosis and skewness of CT densitometry reflect airflow limitation and air-trapping. Higher kurtosis or skewness on expiratory CT scan indicates more severe conditions in smokers.

INTRODUCTION

Kurtosis and skewness, which represent the distortion or disparity deviation of a histogram when compared with a normal distribution, have been previously studied in pulmonary diseases using lung density histograms obtained by computed tomography (CT). Almost all published information on kurtosis or skewness of CT densitometry in the lung has focused on interstitial lung disease (ILD), where lower kurtosis and skewness are observed in patients with more progressed disease (fibrosis) and more compromised lung function (1–7).

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Studies on kurtosis and skewness of the density histogram in subjects with chronic obstructive pulmonary disease (COPD) are much more limited (8, 9). Although several quantitative CT indices, including the percentage of low attenuation area (LAA%) and mean lung density (MLD), are obtained from the CT density histogram and have proven to be significantly associated with lung function (10–18), it remains unclear if kurtosis and skewness of the same density histogram correlate with lung function in individuals with COPD. Furthermore, no previous paper has shown kurtosis and skewness on both inspiratory and expiratory CT scans.

Recently, Matsuoka and colleagues reported that lower kurtosis and skewness of CT densitometry correlate with greater hypoxemia in patients with pulmonary embolism (PE) (19). In both ILD and PE, lower kurtosis and skewness, which suggest heterogeneity of the lung density on CT scans, indicate deteriorated lung function. On the other hand, although no published information is available on quantitative assessment of densitometric heterogeneity in COPD patients, it has been acknowledged that expiratory CT scans of normal subjects often demonstrate inhomogeneous lung density, in particular in the gravity-dependent areas (20). Based upon these observations, it would be of interest to examine whether objective measurements of kurtosis and skewness of the CT lung histogram, which imply heterogeneity of the lung field, are positively or negatively related to airflow limitation or air-trapping in smokers, including COPD subjects. Thus, the aim of this study is to evaluate the relationships between pulmonary function tests (PFT) and kurtosis or skewness of CT densitometry in smokers.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at our institution. The manuscript was reviewed and approved according to the procedures outlined by the Lung Tissue Research Consortium. Further information on the Consortium is available on the website [www.ltrcpublic.com]. The subjects' data utilized in this study were previously analyzed with a different objective for other research (21).

Subjects

CT scans and clinical information for 184 subjects were collected from March 2005 to February 2008, and were provided for this study by the Consortium. All subjects gave written informed consent. Exclusion criteria included the following: (i) usage of CT scanners made by different manufacturers (n = 64), (ii) CT scans with contrast medium or different slice thickness (n = 29), (iii) different tube current or voltage (n = 12), (iv) no available expiratory CT scan (n = 11), (v) no history of cigarette smoking (n = 1), (vi) previous history of lung resection (n = 3), (vii) presence of pneumothorax, lobar atelectasis, large bullae (>3 cm in diameter), severe fibrosis, or a mass (>3 cm in diameter) (n = 18). According to these criteria, a total of 46 smokers (20 females and 26 males; age range 46−81 years) were eventually selected and analyzed in this study. All subjects were current or former

Table 1. Clinical characteristics of 46 subjects

	Mean ± SD	(Range)
Age (years)	67.7 ± 7.9	(46–81)
Smoking index (pack-years)	50.8 ± 38.4	(5–180)
FEV_1 (%predicted)	57.9 ± 24.6	(15–114)
FEV_1/FVC	0.55 ± 0.14	(0.25–0.81)
RV/TLC	0.50 ± 0.12	(0.32–0.73)
DLco (%predicted)	61.6 ± 22.2	(22–103)

FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide.

smokers (mean pack-years, 50.8 ± 38.4; current smokers, n = 4; former smokers, n = 42; respectively). Table 1 summarizes the characteristics of the subjects.

Pulmonary function tests

All 46 subjects performed pre-bronchodilator spirometry, including forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC), according to American Thoracic Society standards as described previously (22). Diffusing capacity for carbon monoxide (DLco) was measured by the single breath method. These values were expressed as the percentages of predicted values. Residual volume (RV) and total lung capacity (TLC) were measured by plethysmography (23). Table 1 summarizes the PFT results.

Except for 6 subjects who did not show any COPD symptoms or abnormal results at pre-bronchodilator spirometry, 40 subjects who were clinically diagnosed with COPD underwent post-bronchodilator spirometry. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging (24), 46 subjects were eventually classified as follows: smokers with normal lung function, n = 6; GOLD stage 1, n = 7; stage 2, n = 19; stage 3, n = 9; and stage 4, n = 5. Due to the small number of subjects, they were eventually categorized into three groups in advance to statistical analyses (Normal, stage 1 or 2, and stage 3 or 4).

Thin-section CT

All subjects were scanned with 16-detector CT (LightSpeed 16 or LightSpeed Pro16, GE Medical Systems, Milwaukee, WI, USA) at full inspiration and full expiration, without receiving a contrast medium. Prior to CT scanning, subjects were coached to hold their breath at full inspiration and full expiration. According to the scanning protocol of the Consortium, images were obtained using 140 kV and 300 mA. The scanning field of view (FOV) ranged from 28 to 44 cm, which was based upon the subject's body habitus. Exposure time was 0.53 s and the matrix size was 512×512 pixels. Images were reconstructed with a 1.25 mm-slice thickness (with 0.625 mm-overlapping), using the "Bone" algorithm.

Measurements of CT indices

The analysis for kurtosis, skewness, and other CT indices was performed using free open-source software (Airway Inspector, Brigham and Women's Hospital, Boston, MA, USA) [www.airwayinspector.org], as described previously (21, 25, 26). The software automatically measured kurtosis, skewness,
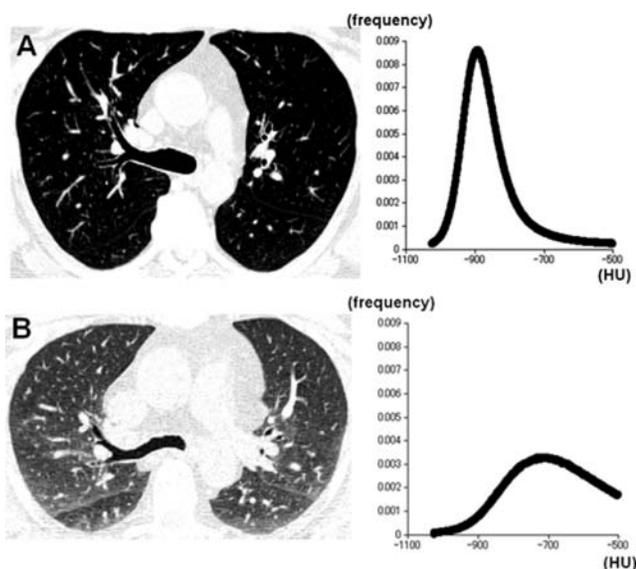
Figure 1. A 60-year-old male smoker with normal lung function (FEV$_1$%predicted = 86%). Inspiratory (**A**) and expiratory (**B**) CT images and the density histograms are demonstrated. On the expiratory CT image (**B**), lung density increased particularly in dorsal parts of the bilateral lungs, resulting in heterogeneous lung density. Although inspiratory kurtosis and skewness are measured as 8.6 and 2.1, expiratory kurtosis and skewness decrease to 2.6 and 0.3. Note that the density histograms are obtained from all axial CT images that include the lung parenchyma, and not by a single image.

LAA% [< −950 Hounsfield unit (HU)], and MLD. In brief, the software (i) segmented the lung parenchyma (−1024 to −500 HU) from the chest wall and the hilum, (ii) created a density histogram for the entire lung parenchyma, and (iii) measured kurtosis and skewness of the histogram. The trachea and the major bronchi were not included in the measured lung parenchyma. Our previous study already reported LAA% and MLD measures of the 46 subjects analyzed in this study (21).

Kurtosis, which demonstrates how sharply peaked a histogram is, is given by the following equation:

$$Kurtosis = \sum n_i(x_i - x)^4 / Ns^4$$

where n_i is the number of pixels at lung attenuation value x_i, x is the mean value of lung attenuation, s is the standard deviation (SD), and N is the total number of pixels.

Skewness, indicating the degree of asymmetry of a histogram, is given by the following equation:

$$Skewness = \sum n_i(x_i - x)^3 / Ns^3$$

Using these equations, a normal distribution has a kurtosis of three and a skewness of zero. The expiratory/inspiratory (E/I) ratios of kurtosis and skewness were calculated.

Figures 1 and 2 show examples of the analysis performed by the software.
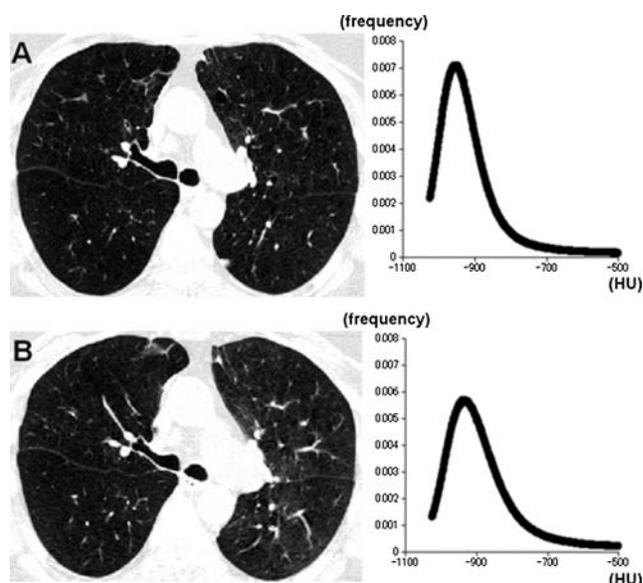
Figure 2. A 62-year-old man with chronic obstructive pulmonary disease (GOLD stage 4, FEV$_1$%predicted = 21%). CT images and the density histograms at full inspiration (**A**) and expiration (**B**) are demonstrated. The changes in kurtosis and skewness are relatively small, suggesting more homogeneous lung density on the expiratory image (inspiratory scan, kurtosis = 10.6, skewness = 2.4; expiratory scan, kurtosis = 7.5, skewness = 1.9, respectively).

Statistical analysis

All statistical analyses were performed using JMP 7.0 software (SAS Institute, Cary, NC, USA). Data were expressed as mean ± SD. The linear regression analysis was used to estimate the relationships between CT measures and PFT values, including pre-bronchodilator FEV$_1$%predicted, pre-bronchodilator FEV$_1$/FVC, RV/TLC, and DLco%predicted. The significance of the differences in expiratory CT values between GOLD- based subject groups was evaluated by one-way analysis of variance (ANOVA), followed by the Bonferroni test for individual comparisons. P values less than 0.05 were considered statistically significant.

RESULTS

CT measurements and correlations with lung function

Table 2 demonstrates CT measurements and their correlations with PFT values. The mean kurtosis decreased from 7.9 ± 2.2 at inspiration to 5.2 ± 1.8 at expiration. Also, the mean skewness decreased from inspiration to expiration (1.9 ± 0.4 at inspiration and 1.3 ± 0.5 at end-expiration).

Although inspiratory kurtosis or skewness did not show significant correlations with FEV$_1$%predicted, FEV$_1$/FVC, RV/TLC, or DLco%predicted, expiratory kurtosis demonstrated significant correlations (p < 0.001) with FEV$_1$%predicted, FEV$_1$/FVC, and RV/TLC (Fig. 3; FEV$_1$%predicted, R = −0.581; FEV$_1$/FVC, R = −0.612; RV/TLC, R = 0.613, respectively). Similarly, expiratory skewness showed significant correlations (p < 0.001) with PFT results (Fig. 4; FEV$_1$%predicted, R = −0.584;

Table 2. CT measurements and correlations with lung function

	CT measurements		Correlations with pulmonary function tests			
	Mean ± SD	(Range)	FEV$_1$ (%predicted)	FEV$_1$/FVC	RV/TLC	DLco (%predicted)
Insp-kurtosis	7.9 ± 2.2	(3.4–12.1)	−0.215	−0.221	0.192	0.122
Exp-kurtosis	5.2 ± 1.8	(2.4–9.0)	−0.581[a]	−0.612[a]	0.613[a]	−0.263
Kurtosis E/I ratio	0.7 ± 0.2	(0.3–1.0)	−0.546[a]	−0.572[a]	0.556[a]	−0.469[b]
Insp-skewness	1.9 ± 0.4	(0.9–2.7)	−0.250	−0.252	0.214	0.094
Exp-skewness	1.3 ± 0.5	(0.2–2.2)	−0.584[a]	−0.619[a]	0.585[a]	−0.240
Skewness E/I ratio	0.7 ± 0.2	(0.1–1.0)	−0.585[a]	−0.612[a]	0.580[a]	−0.328[c]

[a] $p < 0.001$, [b] $p < 0.01$, [c] $p < 0.05$.

Insp, inspiratory; exp, expiratory; E/I, expiratory/inspiratory; FEV$_1$, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide.

FEV$_1$/FVC, R = −0.619; RV/TLC, R = 0.585, respectively). No significant correlations were found between expiratory kurtosis or expiratory skewness and DLco% predicted.

Further, the E/I ratios of kurtosis and skewness demonstrated significant correlations with FEV$_1$%predicted, FEV$_1$/FVC, RV/TLC, and DLco%predicted (Table 2, kurtosis E/I ratio, FEV$_1$%predicted, R = −0.546, p < 0.001; FEV$_1$/FVC, R = −0.572, p < 0.001; RV/TLC, R = 0.556, p < 0.001; DLco%predicted, R = −0.469, p = 0.001; skewness E/I ratio, FEV$_1$%predicted, R = −0.585, p < 0.001; FEV$_1$/FVC, R = −0.612, p < 0.001; RV/TLC, R = 0.580, p < 0.001; DLco%predicted, R = −0.328, p = 0.03, respectively).

Expiratory kurtosis or skewness and the GOLD stages

After it was confirmed by ANOVA that at least a significant difference was included in each multiple comparison model (p < 0.001), the differences in expiratory kurtosis and skewness among all pairs were evaluated. Significant differences in expiratory kurtosis or skewness were observed among all combinations; the group with severe COPD showed higher expiratory kurtosis or skewness (Fig. 5).

DISCUSSION

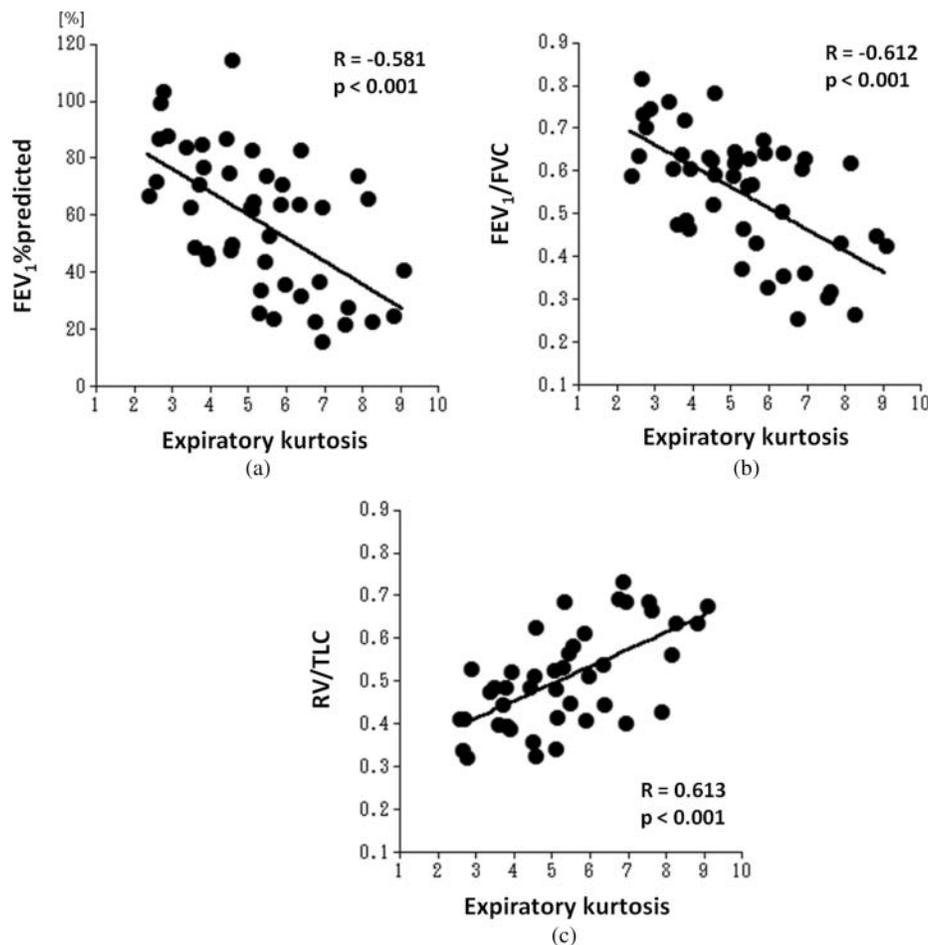In the current study, we found that expiratory kurtosis and skewness of CT density histograms correlate with lung

Figure 3. Correlations between expiratory kurtosis and lung function. Significant correlations (p < 0.001) are observed between expiratory kurtosis and pulmonary function tests (FEV$_1$%predicted, R = −0.581; FEV$_1$/FVC, R = −0.612; RV/TLC, R = 0.613, respectively).
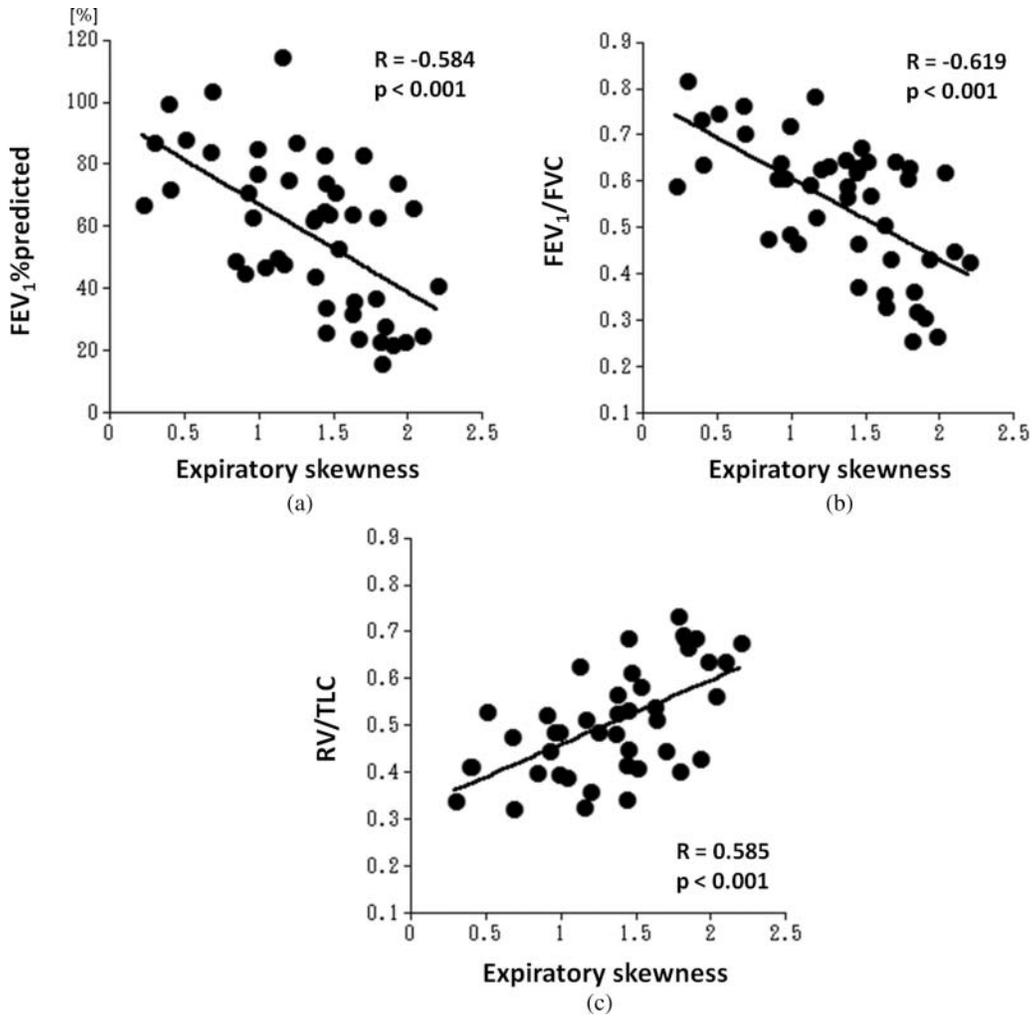
Figure 4. Correlations between expiratory skewness and lung function. Similar to expiratory kurtosis, expiratory skewness shows significant correlations ($p < 0.001$) with pulmonary functions tests (FEV_1%predicted, $R = -0.584$; FEV_1/FVC, $R = -0.619$; RV/TLC, $R = 0.585$, respectively).

Figure 5. Expiratory kurtosis or skewness in the subject groups according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging. Significant differences in expiratory kurtosis (**A**) and skewness (**B**) are observed in all pairs of subject groups. P values are obtained using the Bonferroni test.

function in smokers. Higher kurtosis and skewness on expiratory scans, which suggest a higher peakedness and more right-skew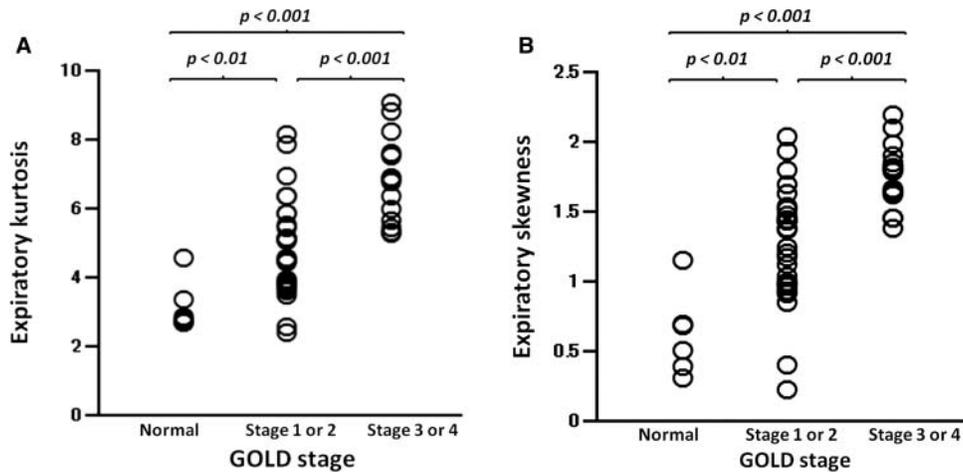ed distribution of the density histogram, indicate more severe expiratory airflow limitation and air-trapping in smokers.

In COPD, multiple papers have described that several indices, such as LAA% and MLD obtained from the same histogram, can predict lung function (10–18). However, except for a texture-based adaptive multiple feature method (AMFM) (8, 9), no published information is available on kurtosis or skewness of CT densitometry in subjects with COPD. In the current study, we first reported that kurtosis and skewness decrease on expiratory scans, particularly in smokers with normal lung function or mild COPD subjects. In severe COPD subjects, in contrast, kurtosis and skewness remain high on expiratory scans.

These differences lead to significant correlations between expiratory kurtosis or skewness and PFT values, including FEV_1%predicted, FEV_1/FVC, and RV/TLC. Compared with our previous study analyzing the same 46 subjects using LAA% and MLD (21), the correlations of expiratory kurtosis or skewness with FEV_1%predicted or FEV_1/FVC are comparable to those of LAA% or MLD. Further, expiratory kurtosis shows higher correlation coefficient with RV/TLC than LAA% and MLD. We believe, therefore, that kurtosis and skewness of the density histogram can be additional CT parameters in analyzing expiratory CT scans in subjects with COPD.

Although it remains difficult to speculate on the exact reasons for the decreases in kurtosis and skewness by expiration, the following explanations are plausible. The decrease in skewness can be partially explained by the increase in MLD, which is directly correlated with decrease in lung volume on expiratory scans (21). As MLD increases with expiration, the right-skewed distribution (large skewness) shifts to higher lung densities, resulting in a decrease in skewness. The decrease in kurtosis, however, is more difficult to explain. In subjects with normal lung function, as is shown in Figure 1, the height of the peak (frequency of the most frequent CT value) of the density histogram tends to decrease significantly on expiratory CT scans. A possible explanation for the phenomenon would be the increased heterogeneity of the lung density.

As is illustrated in Figure 1, on expiratory scans, inhomogeneous, patchy increases in CT density can occur in healthy subjects, particularly in the dorsal (gravity-dependent) lung field. This phenomenon, which has been reported as airtrapping-like appearances in asymptomatic healthy subjects (20), would contribute to the widening of the distribution, which may result in the decrease of kurtosis. To reiterate, it would be predicted that the distribution of air or collapsibility of the pulmonary structures are more heterogeneous and would be influenced by gravity-dependence in the well-exhaled lung, resulting in inhomogeneous CT density of the lungs on expiratory scans in normal subjects. In this situation, the peak of CT density histogram does not move parallel to the right nor maintain its height from inspiratory to expiratory scans. Statistically, however, a distri-

bution with broad edges does not always demonstrate higher kurtosis, and therefore these explanations are speculative.

Measuring kurtosis and skewness of CT density histograms has been mainly the subject for detailed study in ILD (1–7). In these studies, lower kurtosis and skewness is found in those subjects with the greatest functional impairment. Although the direct relationship between the degree of fibrosis in the lung and decrease in kurtosis or skewness of CT density histograms has not been pathologically investigated, it is generally accepted that decreases in kurtosis or skewness reflect fibrotic changes in the lung caused by ILD (1–6, 27). Decreases in kurtosis or skewness have also been reported in patients with PE and cystic fibrosis (19, 28), where lower kurtosis or skewness is correlated with severe hypoxemia in PE and with severe airflow limitation in cystic fibrosis. In contrast to these diseases, our observations indicate that lower values of kurtosis or skewness on expiratory scans reflect better lung function in subjects with COPD, which would be of interest for future studies of density histograms in various pulmonary diseases.

Although measurements of kurtosis and skewness did not show a clear correlative advantage to more standard densitometric measures of emphysema when predicting lung function, we think that these measures may be applied to future CT studies for other pulmonary disorders. For example, it has been acknowledged that partial air-trapping (mosaic pattern) is frequently observed on CT scans in subjects with bronchiolitis obliterans (BO) after stem cell transplantation, and visual scores of air-trapping correlate with lung function (29–32). It would be of interest whether those air-trapping scores are expressed by kurtosis or skewness of the density histogram.

We recognize some important limitations in this study. First, the number of the subjects in the current study was relatively small. Compared with previous studies (11, 14), the 46 subjects analyzed in this study demonstrated higher correlation coefficients between several CT indices and airflow obstruction (21). Considering the fact that airflow obstruction is also caused by airway abnormalities, the small number of subjects might have amplified those observations.

Second, on the CT densitometry, the lower threshold of −500HU for determining the lung parenchyma needs further evaluation. Although several previous papers have used the same threshold both for inspiratory and expiratory CT scans in COPD (11, 16, 17), a higher threshold has also been recommended for expiratory scans (10). Although we think the changes in the upper threshold would limit the study to a minor degree, future investigation is needed to determine an optimal upper threshold of the CT densitometry.

Third, measurements of kurtosis and skewness did not show a clear correlative advantage to more standard densitometric measures when predicting lung function (21). Currently, measurements of kurtosis and skewness seem to act simply as additive values in CT studies for COPD. However, to evaluate inhomogeneous "mosaic" patterns in various lung diseases, we believe that measurements of kurtosis and skewness on density histograms have potential for future CT studies.

Fourth, according to the scanning protocol determined by the Lung Tissue Research Consortium, a relatively high dose of radiation and a sharp reconstruction kernel were used in this study. Since it has been acknowledged that radiation dosage does not influence kurtosis or skewness measures severely (7), it is recommended to apply a low-dose technique to future studies for CT-based lung analyses.

Fifth, since six smokers with normal lung function did not undergo post-bronchodilator spirometry, we utilized the data of pre-bronchodilator spirometry for assessing airflow limitation. Because the GOLD staging is based on post-bronchodilator spirometry, it is recommended to evaluate the correlations of kurtosis or skewness with results of post-bronchodilator spirometry for future COPD studies.

Sixth, ILD sometimes coexists with emphysema in COPD subjects, known as smoking related ILD. Although we excluded severe fibrosis subjects from this study, it can be predicted that slight fibrosis such as smoking-related ILD would have coexisted in the subjects we analyzed, resulting in amplified lower kurtosis or skewness.

In summary, we first reported that expiratory kurtosis and skewness of CT densitometry correlate airflow limitation and air-trapping in COPD. Furthermore, the E/I ratios of kurtosis and skewness are also correlated with lung function. Although it has been reported that lower kurtosis or skewness indicates deteriorated lung function in ILD or PE, higher kurtosis or skewness on expiratory CT scan suggests more severe airflow limitation and air-trapping in COPD.

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